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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,764	11/15/2000	Heinz-Josef Lenz	13761-0739	7045

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,764	LENZ ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 47-60 and newly added claims 61-67 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 102

3. Claims 57-59 are rejected under 35 USC 102(b) as being anticipated by New England Biolabs catalog (1996, page 102).

New England Biolabs teaches a kit which contains a DNA ladder X174 DNA-Hae III Digest which contains base pairs on the order of 1,353 base pairs to 72 base pairs. Alternatively, New England Biolabs teaches a kit which contains a DNA ladder pBR322 DNA-BstN I Digest which contains base pairs on the order of 1, 857 to 13 base pairs (see page 102). Either of these DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 58. Additionally, the DNA ladder is provided in a solution of 10 mM Tris and 1mM EDTA (claim 59). It is noted that the use for the kit and the instructions for the kit carry no

patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..."

Response to Arguments

4. The response asserts that the kit contains a means for determining a genomic polymorphism of the 5' UTR of the TS gene and that nothing in the Biolabs indicate that the markers would specifically recognize a genomic polymorphism of the 5' UTR of the TS gene. This argument has been thoroughly reviewed but was not found persuasive. Firstly, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., specifically recognize a genomic polymorphism) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Secondly, the ladders taught by New England Biolabs can be used as size markers. The genotyping assay as taught in the specification uses PCR amplicon size to determine genotype. The response's assertion with regard to the instructions for the kit have been thoroughly reviewed but are not persuasive. As already noted in the previous office action: The components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and

the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..." Applicant's are directed to the MPEP. As stated in the MPEP, 2112.01 III: "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 03-1524 (CAFC 2004)". In the instantly claimed kit, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. For these reasons and the reasons already made of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

5. Claims 57-60 are rejected under 35 USC 103(a) as being unpatentable over of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya and further in view of Erlich (US Patent 5,468,613) and New England biolabs.

The teachings of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya are set forth in the previous office action. Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya do not teach a kit comprising DNA tandemly repeated sequence of the TS gene, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40). Further, Erlich teaches providing kits which include such sequence specific oligonucleotides. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct sequence specific oligonucleotides as taught by Erlich that contained tandemly repeated sequences of the TS gene for use in the method of Horie &

Leichman, in view of Ruano, and further in view of Wilson or Tamiya for the purpose of providing a sequence specific oligonucleotide that could be used to determine a tumor cell's TS genotype in the screening method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya more convenient to perform. It would have been further obvious to provide the oligonucleotides in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that he use for the kit and the instructions in the kit carry no patentable weight. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Response to Arguments

6. The response traverses the rejection. The response asserts that none of the cited references teach the necessary correlation between the genotype of the sample to be tested and the predictive response. The response asserts that this information is more than merely providing instructions to the user, it allows correlation between laboratory information and clinical relevance. This argument has been thoroughly reviewed but was not found persuasive. The components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter.

All the printed matter does is teach a new use for an existing product..." Applicant's are directed to the MPEP. As stated in the MPEP, 2112.01 III: "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 03-1524 (CAFC 2004)". In the instantly claimed kit, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. Applicants assertion with regard to the kit only containing information on how to carryout one or more genotyping methods has been thoroughly reviewed but was found unpersuasive because such kit comprising only printed material is considered non statutory and is not patentable subject matter. For these reasons and the reasons already made of record, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Written Description

7. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Newly added claim 67 recites "wherein the subject suffers from a cancer selected from ... liver cancer". A thorough review of the specification and the originally filed claims fails to provide support for the broad recitation of liver cancer. Liver cancer encompasses, for example,

HCC. While the specification teaches analysis of metastatic liver tumor sample in colorectal cancer patients, such recitation does not provide support for any liver cancer, including primary liver tumors. Accordingly, the specification as originally filed does not to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Claim 47-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said gene expression" in claim 47 lacks antecedent basis. The method lacks a step of determining gene expression. Accordingly, the step of correlating lacks antecedent basis to an active step in the method. As such, the claim further lacks a step relating back to the preamble. It is unclear therefore, it the claim is drawn to a method of screening a subject for sensitivity to a chemotherapeutic drug, or a method of genotyping.

Claim Rejections - 35 USC § 102

9. Claims 47-50, 61, 62, and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Horie.

The claims have been broadly interpreted to encompass a method of genotyping the thymidylate synthase gene. Horie teaches a method of analyzing the DNA polymorphism of the tandemly repeated sequences in the 5' terminal regulatory region of the TS gene in genomic DNA from leukocyte samples from normal patients (see abstract, and page 192, col. 2).

10. Claims 47, 48, and 61-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Govindarajan (Govindarajan et al. Proc. Annu. Meet Am. Soc. Clin. Oncol. 1998, 17; A2178, meeting abstract).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

11. Claims 47-48, and 61-66 are rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by Howells (Howells et al; Clinical Cancer Research, vol. 4, pp 2439-2445; October 1998).

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (p=.004) (see abstract, page 2443, col. 1, first para).

Claim Rejections - 35 USC § 103

12. Claims 47-56 and 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, and further in view of, in the alternative, Govindarajan or Howells.

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells

teaches genotyping for the null alleles using PCR on DNA isolated from blood or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to chemotherapy drugs. The ordinary

artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches that it is possible to create a prognostic test for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development. Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug. Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, and 4) TS genotype could be determined for a subject from normal cells, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from the subject's normal cells for the purpose of determining if a genotypic assay could be used as a prognostic indicator of response

to 5-FU therapy in patients with colorectal cancer. Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

13. Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, and further in view of, in the alternative, Govindarajan or Howells as applied to claims 47-56 and 61-67 above, and further in view of Erlich (US Patent 5,468,613) and New England biolabs.

The teachings of Horie and Leichman in view of Ruano, and further in view of Govindarajan or Howells are set forth above. Horie & Leichman, in view of Ruano, and further in view of Govindarajan or Howells do not teach a kit comprising DNA tandemly repeated sequence of the TS gene, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40). Further, Erlich teaches providing kits which include such sequence specific oligonucleotides. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct sequence specific oligonucleotides as taught by Erlich that contained tandemly repeated sequences of the TS gene for use in the method of Horie &

Leichman, in view of Ruano, and further in view of Govindarajan or Howells for the purpose of providing a sequence specific oligonucleotide that could be used to determine a subject's TS genotype in the screening method of Horie & Leichman, in view of Ruano, and further in view of Govindarajan or Howells. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of providing pre-weighed, premeasured reagents that would make the method of Horie & Leichman, in view of Ruano, and further in view of Govindarajan or Howells more convenient to perform. It would have been further obvious to provide the oligonucleotides in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that he use for the kit and the instructions in the kit carry no patentable weight. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. No claims are allowable over the cited prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

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5/27/05